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*Report*

# Evaluation of a Noninvasive Method for Monitoring Percutaneous Absorption of Lidocaine *in Vivo*

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The pharmacodynamic measurement of *in vivo* skin penetration of lidocaine was explored with an instrument used in dentistry to determine tooth pulp vitality. The instrument delivers a low-current, pulsatile electrical waveform of increasing intensity with time. The readings, which are reproducible, are in arbitrary units on a scale of 0–80. Testing of naive sites showed variation as a function of location, even over relatively small distances. The response at a marked site over a 12-hr period generally was consistent in five subjects. Following intradermal administration of 1 or 2% lidocaine hydrochloride injection in one subject, the instrument reached its maximum value within 2 min. This was followed by a sustained plateau and then a gradual falloff of the effect. Topical formulations containing 5% lidocaine base and corresponding blank formulations were applied under occlusion within Hilltop chambers to intact skin on the forearms of human volunteers for 3 hr. While the response to a 40% propylene glycol formulation was not significantly different from the corresponding control, a cream exhibited slow development of profound anesthesia that lasted for several hours following chamber removal.

KEY WORDS: topical anesthesia; pharmacodynamic testing; percutaneous absorption; lidocaine.

## INTRODUCTION

One approach to measurement of skin penetration of biologically active compounds *in vivo* relies on the observation of some physiologic or pharmacologic response within the skin. Local anesthetics as a group lend themselves to *in vivo* study, as attested to by the wide variety of pharmacologic screening tests in the literature (1–6). These compounds produce an easily observable pharmacologic event marking their transport to the site of action—the development of anesthesia. By testing for the lack of response to an appropriate stimulus, local anesthetics can serve as markers for determining the effects of formulation components on the permeability characteristics of the skin *in vivo*. In principle, this is quite similar to the use of the vasoconstrictor assay for topical steroids (7,8).

Although generally considered inactive when applied to intact skin, local anesthetics have been useful in producing anesthesia of mucous membranes and damaged skin (9–11). Recent reports have indicated that induction of profound anesthesia after topical application may be achieved from alcoholic (12), emulsion (13), or eutectic (14) formulations.

Any reliable method of evaluating the pain response must meet three criteria: the stimulus must be measured in physical units to permit quantitation and comparisons; the sensation produced must be clearly detectable; and tissue damage should ideally be absent or minimized (15).

Test methods involving pin pricks are widespread (2,3); however, it is difficult to quantitate or reproduce the stimuli. In addition, pin pricks can damage the skin at the test site, possibly altering the absorption process. Thermal radiation, from either a high-intensity lamp (5) or a laser (16), has been used as a test stimulus. Controlled electrical stimulation has been employed successfully in evaluating and ranking topical anesthetic formulations applied to mucosa (10) and normal and damaged skin (11) and appears to satisfy the three criteria best.

This report introduces a novel electrometric technique capable of quantitating the development of local anesthesia. The device is hand-held, portable, easily operated, and commercially available. The sensation produced is distinct. The response to the device is reproducible and is displayed digitally. The voltage and current employed are low, minimizing the risk of skin damage.

Table I. Variation in Instrument Reading at Naive Body Sites (Mean ± SD; $n$ = 10 Readings)

| Site | Instrument reading |
|---|---|
| Forehead | 48 ± 3.1 |
| Lower lip | 44 ± 4.2 |
| Chest | 49 ± 2.6 |
| Upper arm | 45 ± 1.6 |
| Abdomen | 49 ± 2.3 |
| Forearm | 60 ± 1.3 |
| Fingertip (index) | 62 ± 3.6 |
| Ankle | 66 ± 4.2 |

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Table II. Instrument Readings for Left and Right Forearms in One Subject ($n$ = 3 Readings)

| Mean instrument reading (SD) | | | | | |
|---|---|---|---|---|---|
| Left arm | | | Right arm | | |
| Radial | Medial | Ulnar | Ulnar | Medial | Radial |
| 61 (4.4) | 50 (1.5) | 51 (3.5) | 48 (4.2) | 55 (1.5) | 62 (1.0) |
| 52 (1.2) | 57 (2.5) | 52 (2.1) | 54 (3.1) | 57 (3.2) | 53 (1.0) |
| 57 (1.0) | 62 (0.6) | 54 (2.6) | 56 (2.6) | 65 (1.0) | 53 (2.5) |
| 60 (4.0) | 60 (1.5) | 47 (1.0) | 45 (3.2) | 58 (2.9) | 54 (1.0) |
| 52 (3.1) | 62 (3.0) | 52 (1.5) | 50 (2.1) | 60 (2.9) | 41 (2.3) |
| 45 (4.0) | 62 (2.6) | 44 (2.6) | 57 (3.0) | 57 (2.1) | 45 (2.0) |
| 51 (3.1) | 43 (6.1) | 43 (6.1) | 57 (1.5) | 44 (1.0) | 47 (1.2) |
| 48 (1.0) | 48 (1.2) | 66 (2.3) | 42 (4.6) | 47 (3.1) | 47 (2.5) |
| 52 (3.5) | 59 (3.1) | 50 (2.1) | 46 (2.1) | 59 (2.1) | 50 (2.6) |
| 53 (4.2) | 53 (2.0) | 65 (3.8) | 47 (3.1) | 46 (0.6) | 53 (3.2) |
| 39 (1.0) | 46 (0.6) | 42 (2.6) | 42 (1.7) | 49 (0.6) | 37 (1.2) |
| 53 (2.5) | 52 (1.2) | 46 (2.0) | 42 (3.5) | 48 (4.0) | 50 (2.6) |

## MATERIALS AND METHODS

### Chemicals

The following chemicals were obtained directly from the manufacturer and used without further purification: lidocaine base (Sigma Chemical Co., St. Louis, MO), propylene glycol (J. T. Baker, Phillipsburg, NJ), hydroxypropyl cellulose (Klucel LF, Hercules, Wilmington, DE), chlorobutanol (Eastman Kodak, Rochester, NY), light mineral oil (Fisher Scientific, Fair Lawn, NJ), emulsifying wax (Polawax, Croda, New York, NY), 0.9% sodium chloride injection, USP (Abbott, Chicago, IL), and 1 and 2% lidocaine hydrochloride injection, USP (Elkins–Sinn, Cherry Hill, NJ). Hilltop Chambers (0.95 $cm^2$) were a gift from Hilltop Research, Inc. (East Brunswick, NJ).

### Topical Formulations

All formulations were prepared on a weight/weight basis. The standard formulation consisted of a suspension of lidocaine base (5.0%) in 40.0% propylene glycol, gelled with 1.0% hydroxypropyl cellulose, and preserved with 0.25% chlorobutanol. The final pH was adjusted to 7.9 with 0.1 $N$ sodium hydroxide or 0.1 $N$ hydrochloric acid.

The cream base, an oil-in-water emulsion, was prepared from 18% emulsifying wax, 4.5% light mineral oil, and 77.5% water (13). Lidocaine base (5.0%) was levigated into the cooled cream.

Blank formulations identical in all respects to the active formulations except for the omission of lidocaine were also prepared in the same manner.

### Instrumentation

The Vitality Scanner (Analytic Technology, Redmond, WA) is commercially available to dentists for assessing the vitality of tooth pulp (17–20). The hand-held device delivers a current of 0.1 mA through a 2-mm-diameter flat-surface metal probe. The instrument turns on automatically when electrical contact is made. Voltage increases slowly from 15 V to a maximum of 300 V; the rate of increase is controlled by presetting an instrument dial. The electrical stimulation is delivered as a burst of 10 pulses of negative polarity, each pulse lasting about 150–200 μsec, with a 3- to 15-msec pause between pulses. The delivery of each burst advances the digital counter on the instrument, to a maximum of 80 (21).

### Selection of Subjects

The study was approved by the Institutional Review Board of Rutgers University, and all subjects gave written informed consent prior to participation in the study. Six (five male, one female) healthy subjects over 18 years of age were selected for participation. All subjects denied allergy to lidocaine or any other local anesthetic, marked sensitivity to soaps or detergents, presence of any skin diseases, heart disease, an implanted pacemaker, and, if female, pregnancy or breastfeeding.

### Subject Training

Each subject was instructed in the testing technique. Instrument requirements for proper circuit formation were best met when the subject applied the probe. Under super-

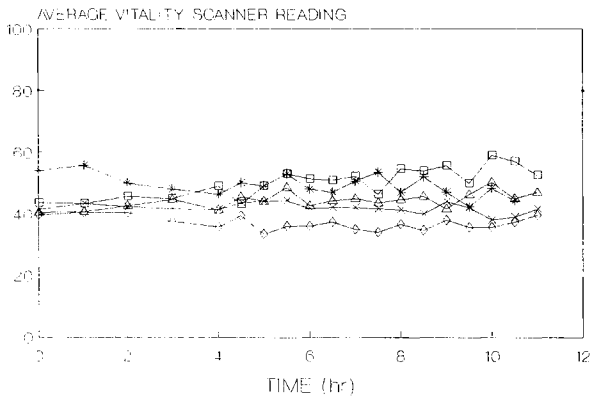


Fig. 1. Mean instrument reading over time at naive sites on the volar forearms of five subjects. Bars indicate SE of three readings. Subject 001 (◇), 002 (△), 003 (*), 005 (□), and 006 (×).

Table III. Instrument Readings at Marked Sites on Volar Forearms of Five Subjects Over Time

| Subject No. | $n$ | Mean instrument reading (SD) at site 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| 001 | 60 | 46 (4.0) | 45 (5.4) | 42 (2.7) | 39 (3.1) |
| 002 | 60 | 51 (5.2) | 44 (2.6) | 45 (5.4) | 44 (3.3) |
| 003 | 54 | 50 (7.0) | 47 (9.5) | 59 (6.3) | 49 (4.2) |
| 005 | 60 | 49 (9.3) | 54 (7.1) | 46 (8.7) | 51 (5.3) |
| 006 | 60 | 63 (3.7) | 42 (2.1) | 44 (3.6) | 53 (4.5) |

vision, the subject placed the probe tip (moistened with 40% propylene glycol) against the skin of the forearm. The subject removed the probe from contact with the skin and informed the investigator when a sensation, usually described as a mild buzz, was first felt. The subjects were not permitted to see the digital display of the instrument.

When the subject was comfortable with handling the device, (s)he tested four sites of skin five times each. Subjects that exhibited inconsistent or nonreproducible results at this point were rejected (subject 004, female).

### Testing of Topical Formulations

Four test areas were selected on the volar surface of each forearm. Each formulation (active and blank) was applied for 3 hr using a Hilltop chamber. Pairs of chambers loaded with blank and active formulations were applied to corresponding sites on both arms. Sites were matched according to anatomic location and response to the Vitality Scanner. Neither the subject nor the investigator knew which of the pair contained the local anesthetic. Sites were assigned to the formulations in a randomized fashion.

At least three replicate measurements were obtained at each marked site at each testing interval. The sites were tested in random order before chamber application, after a half-hour acclimatization period using chambers loaded with blank 40% propylene glycol formulation, hourly during the application period, then every half hour for up to 9 hr after removal of the chambers.

## RESULTS AND DISCUSSION

### Preliminary Testing

Before testing of the topical formulations could begin, it was necessary to characterize the performance of the Vitality Scanner and the response at untreated sites.

Eight widely different body sites on one subject were tested 10 times each with the Vitality Scanner. The mean instrument readings were different, but quite reproducible at any one site, with a standard deviation ranging from 1.3 to 4.2 units (Table I). The most likely factors responsible for the regional variation in instrument reading are differences in stratum corneum thickness, morphology, and chemistry at different sites (22) and nonuniformity in the distribution of the nerve network subserving the skin (23).

A more thorough exploration of the site variation was conducted in the same individual. The forearms were selected due to ease of access as test sites. Responses to the Vitality Scanner were measured over a 1.5 × 1.5-cm grid marked in the central region of both forearms (Table II), avoiding the regions within 4 cm of the wrist and the antecubital fossa. The variation persisted over small distances, but the similarity in pattern of responses over both arms was notable. The paired sites with the greatest mismatch tended to be toward the outer edges of the test area. The central portions corresponded well. A similar correspondence was seen in other subjects. Because of these results further testing was conducted along the midline of the forearm surface.

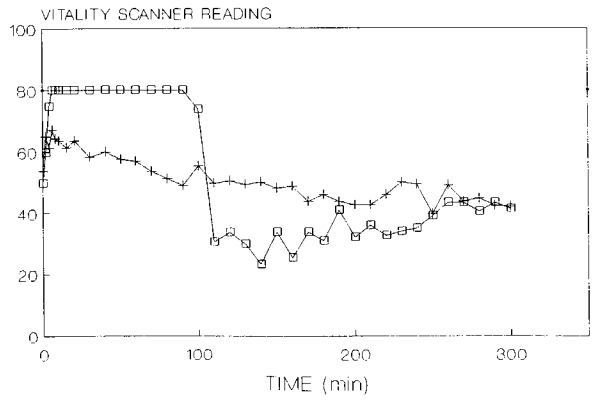


Fig. 2. Mean instrument reading following intradermal administration of 0.1 ml 1% lidocaine HCl (□) or 0.9% NaCl (+). $n$ = 3 readings.

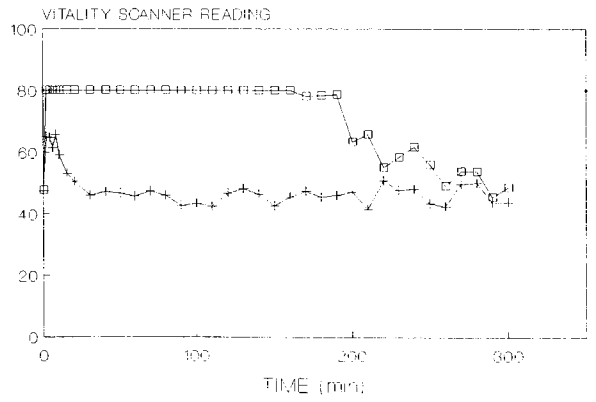


Fig. 3. Mean instrument reading following intradermal administration of 0.1 ml 2% lidocaine HCl (□) or 0.9% NaCl (+). $n$ = 3 readings.

Table IV. Onset and Duration of Anesthesia After Intradermal Injection of 0.1 ml of 1 or 2% Lidocaine HCl for Injection

| Trial | 1% | | 2% | |
|---|---|---|---|---|
| | Onset (min)[a] | Duration (min)[b] | Onset (min)[a] | Duration (min)[b] |
| A | 2 | 48 | 2 | 98 |
| B | 6 | 84 | 2 | 128 |
| C | 2 | 98 | 2 | 158 |

[a] Time to reach maximum Vitality Scanner reading (80) for three repeat measurements.
[b] Total time mean Vitality Scanner reading is maximum (80).

The good correspondence of both arms allowed direct comparison of measurements made on paired sites, with an active formulation on one arm and the blank formulation, serving as a control, on the opposite arm.

The instrument reading at naive, untreated sites on the volar surfaces of five volunteers was obtained periodically for up to 12 hr (Fig. 1). At least three readings were taken at any testing time. Table III gives the instrument readings at all four sites tested on each of the five subjects. As expected, different sites and subjects showed different mean readings. The readings were reasonably consistent, with some random fluctuation appearing in the baseline values over time.

### Intradermal Anesthesia

The performance of the device was also tested in obtunded sites. Intradermal injections of 0.1 ml of 1 or 2% lidocaine hydrochloride for injection and corresponding 0.9% sodium chloride for injection blanks were made in the forearms of one volunteer. Testing was performed every 2 min for 10 min, every 5 min for 10 min, then every 10 min for the remainder of the 5-hr period. Typical results are shown in Figs. 2 and 3. Full anesthesia as indicated by maximal instrument reading and absence of sensation was demonstrated at 2 min for all of the 2% trials and two of the 1% trials. The remaining site did not reach maximum instrument reading until 6 min and may be a result of poor injection technique. The presence of the fluid bleb within the skin decreases the skin's sensitivity to the electrical stimulation,

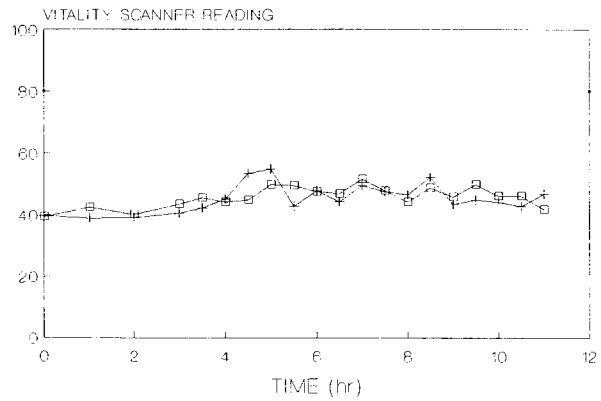


Fig. 4. Mean instrument reading after treatment with blank (+) and lidocaine-containing 40% PG formulation (□). Formulations applied to volar forearms for 3 hr. $n = 3$ readings.

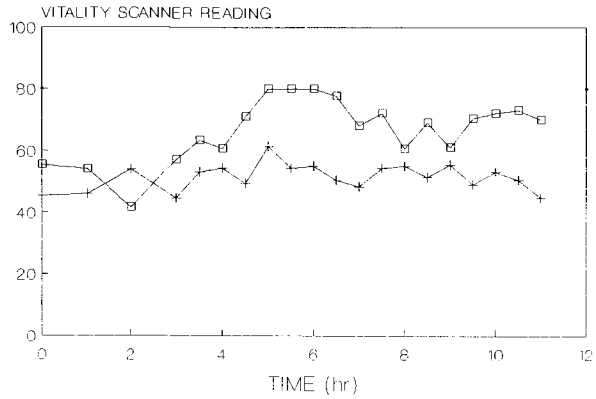


Fig. 5. Mean instrument reading after treatment with blank (+) and lidocaine-containing cream formulation (□). Formulations applied to volar forearms for 3 hr. $n = 3$ readings.

giving a greater response. This is clearly illustrated in the saline injection curves in Figs. 2 and 3. All blebs were resorbed by 10 min; responses at the salient sites returned to baseline levels as the bleb disappeared. Table IV lists the onset times and durations of maximal instrument reading as determined by the Vitality Scanner in three separate trials. The average duration for the 2% solution was 72% greater than for the 1% solution.

### Topical Formulations

Typical response profiles for the propylene glycol and cream formulations are shown in Figs. 4 and 5. The average instrument readings of the active and blank formulations over the 5-hr period immediately following removal of the chambers were compared (Table V). Statistical testing via a paired $t$ test across individuals showed no difference between the propylene glycol formulation containing lidocaine and its blank but a significant difference ($0.01 < P < 0.005$) between the cream and its blank. It is of note that the peak instrument reading was reached 2 or 3 hr after removal of the lidocaine cream in some subjects, indicating that the absorptive process was still occurring. The anesthesia produced was prolonged. The average instrument reading was maintained at 75 or greater for 1.5 hr in one subject and 3 hr in another.

## CONCLUSIONS

The utility of the Vitality Scanner in testing local anes-

Table V. Comparison of Active and Blank Formulations

| Subject No. | Instrument reading difference[a] | |
|---|---|---|
| | 40% PG dispersion | Cream |
| 001 | −1.28 | 30.40 |
| 002 | 0.06 | 17.31 |
| 003 | −11.72 | 11.50 |
| 005 | 3.05 | 11.23 |
| 006 | 3.90 | 25.44 |

[a] Mean instrument reading at active formulation site minus mean instrument reading at blank formulation site.

thesia has been demonstrated. Response to the device varies significantly with test location, even over small distances, but is reproducible at any one site. Testing of sites anesthetized by intradermal injection of lidocaine hydrochloride solutions showed rapid development of profound anesthesia and a prolonged plateau representative of the maximum response of the instrument. The device is capable of monitoring the development of local anesthesia following topical application of lidocaine formulations as a noninvasive pharmacodynamic technique. The maximal instrument reading of 80 may be a limitation, serving to equalize effective formulations. Blank formulations containing no lidocaine do not show the development of any anesthesia. Together, a local anesthetic and the Vitality Scanner can be used to evaluate formulation effects on transport *in vivo*.

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